REMARKS

Claims 4, 6-9, and 16-18 are pending. Claims 4 and 16 have been amended, and support for the amendments can be found at least at page 4, line 2; in example 2 at pages 16 and 17; and at SEQ ID NO:8. No new matter is added by the amendment.

A Supplementary Information Disclosure Statement is enclosed. Applicants respectfully request that the Examiner consider the cited references and indicate that she has done so by returning an initialed copy of the SB08 to Applicants representatives.

A certified copy of priority document PCT/DE00/00244, filed January 29, 2000, is enclosed.

35 U.S.C. § 112, first paragraph (written description)

Claims 4 and 6-9 remain rejected as failing to comply with the written description requirement. This is a new matter rejection.

The claims are directed to isolated oligoribonucleotides having a double stranded structure (dsRNA) consisting of two separate non-linked complementary RNA strands, wherein the dsRNA is 21 nucleotides in length. The PTO stated that

> [w]hile the working examples do disclose use of a single 21 nucleotide RNA, the strands of this RNA are connected by a non-nucleotide linker; therefore RNA of the recited length appears only in the context of covalently linked strands. The specification does not contemplate a limitation wherein the dsRNA is both 21 nucleotides in length and consists of separate non-linked strands and hence does not provide support for such.

Office Action at page 3, last paragraph.

Applicants maintain that there is adequate support in the specification for a dsRNA 21 nucleotides in length and consisting of two separate non-linked strands.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the thing claimed. See, *e.g.*, Moba, B.V. v. Diamond Automation,

Inc., 325 F. 3d 1306, 1319 (Fed. Cir. 2003), and Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563. See also MPEP 2163(I).

Applicants maintain that the specification shows possession of 21 base pair dsRNAs lacking a linkage. The example at page 17, lines 9-27, provides an example of a dsRNA 21 base pairs in length. While in that embodiment, the strands of the dsRNA are linked, elsewhere, the specification is quite clear that the strands can be non-linked, as currently claimed. The specification supports dsRNAs 15-49 nucleotides in length, *e.g.*, 21 nucleotides in length, and supports a dsRNA of any length within the 15-49 nucleotide range (*e.g.*, 21 nucleotides) that is linked or non-linked.

The specification provides dsRNAs of several topologies, including non-linked strands, linked strands, and hairpin configurations. It is quite clear that the application conveys possession of dsRNAs having non-linked strands. For example, at page 4, line 26, of the specification, it is disclosed that "the double-stranded structure is formed by two separate RNA strands or by autocomplementary regions..." Furthermore, the application discloses that dsRNA, composed of separate strands, can have an additional linker. For example, the paragraph spanning pages 4 and 5 of the specification states that "to inhibit dissociation in a particularly effective fashion, the cohesion of the complementary region II, which is caused by the nucleotide pairs can be increased by at least one, preferably two, further chemical linkages." Emphasis added. "Can," as used in this context, is permissive. The product can have a further linkage, but in other embodiments, it will not have even one.

Review of written description must be conducted from the standpoint of one of ordinary skill in the art. MPEP 2163(II)(A)(2). One of ordinary skill in the art would not read the specification to suggest that the optional chemical linkage must be used with dsRNAs of any particular length. Rather, one of ordinary skill would read the specification to disclose that a chemical linkage may be used with any dsRNA disclosed in the application.

The presence of the chemical linkage in the 21 nucleotide example does not eliminate from the disclosure of the originally filed invention the embodiment of "linked and non-linked dsRNA." The linkage in the 21 nucleotide example is simply an exemplification of a single

embodiment. Applicants have used one of the features of this embodiment, strand length of 21 nucleotides, as an example of support for the amended length limitation of 21 nucleotides. There is nothing in the Example that suggests that the only way Applicants viewed that such agents could be made and used were as chemically linked molecules (as suggested by the PTO). It is clear that the inventors contemplated that additional chemical linkages were optional elements.

The conclusion that one of ordinary skill would not immediately understand the specification to disclose both linked and non-linked embodiments of the lengths disclosed (*e.g.*, 21 nucleotides), ignores the plain language of the specification. One of ordinary skill in the art would have immediately recognized this disclosure and would have understood that Applicants were in possession of an unlinked 21 nucleotide long dsRNA.

Given the disclosure of the specification and the level of skill in the art, it is clear that the specification conveys possession of the claimed invention.

As noted above, a dsRNA 21 nucleotides in length, and having non-linked strands, is also disclosed in priority application PCT/DE00/00244. Therefore, the claims are supported at least by the specification of the priority application, filed January 29, 2000. The present application is therefore at least entitled to the priority filing date of January 29, 2000. A certified copy of this priority document is attached.

In view of the foregoing arguments, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 4 and 6-9 under 35 U.S.C. § 112, first paragraph, for failure to satisfy the written description requirement.

35 U.S.C. § 102

Claims 4 and 6-9 remain rejected under 35 U.S.C. § 102(b) as being anticipated by Elbashir (Nature 2001) and under 35 U.S.C. § 102(e) as being anticipated by Tuschl *et al.* (WO 02/44321).

The PTO maintains these rejections based on the incorrect priority date of July 2, 2003. As discussed above, Applicants are entitled to the priority date of PCT/DE00/00244, filed January 29, 2000. Elbashir *et al.* and Tuschl *et al.* are therefore not available as prior art, and

Applicants respectfully request that the rejections under 35 U.S.C. § 102 over these references be withdrawn.

Claims 4 and 6-9 were rejected under 35 U.S.C. § 102(b) as being anticipated by Crooke (U.S. 6,107,094). Applicants respectfully traverse the rejection.

Crooke discloses oligomeric compounds for the purposes of inhibiting gene expression. Crooke is about antisense RNAs: single-stranded RNAs that bind a target RNA, such that the resultant double-stranded structure is degraded by dsRNAses. See, for example, the paragraph spanning columns 9 and 10; column 10 in the first sentence of the third full paragraph; and column 11 in the second and third paragraphs.

The PTO referred to a passage at column 14 where Crooke discloses that the oligonucleotides are preferably from 15 to 25 nucleotides in length. Office Action at page 8. This disclosure is to a single stranded construct and thus does not anticipate the claims, which require a double stranded structure.

The PTO also referred to the 17 and 20 base pair long dsRNAs described at example 27-a at column 50 and in Table 1 at column 5. Crooke used these dsRNAs as substrates to test dsRNAses present in rat liver cytosolic and nuclear extracts (see column 51 in the first paragraph). None of the substrate dsRNAs used described in this example were 21 base pairs in length as required by the claims. Thus, even if double stranded, this disclosure does not anticipate the claims. Further, there is no indication in Crooke that the exemplary dsRNAs described in Table 1 would be useful for specifically inhibiting the expression of a mammalian target gene. There is no indication in Crooke that the inventor ever even contemplated such a use for a dsRNA substrate.

Crooke disloses the use of modified single stranded antisense RNAs for inhibiting target gene expression. There is no teaching or suggestion in Crooke to use a double-stranded RNA to silence gene expression as required by the claims. Thus, Crooke does not anticipate the claims, nor are the claims obvious in view of Crooke.

In view of the forgoing, Applicants respectfully request that the rejection of claims 4 and 6-9 under 35 U.S.C. § 102(b) over Crooke be withdrawn.

35 U.S.C. § 103

The PTO maintained the rejection of claims 16-18 under 35 U.S.C. § 103(a) as being unpatentable over Agrawal *et al.* (WO 94/01550, of record). Applicants again respectfully traverse the rejection.

Agrawal *et al.* teaches oligonucleotides useful for antisense therapeutics that comprise (i) a target hybridizing region and (ii) a self-complementary region. Agrawal *et al.* does not teach or suggest a dsRNA 21 base pairs in length having a complementary region within the dsRNA formed by two separate RNA single strands as required by the claims.

The PTO stated that "On page 15, line 26 through page 17, line 12 Agrawal *et al.* disclose that the self-complementary region of the oligonucleotide is fully or partially complementary to the hybridizing region, the hybridizing region and the self-complementary region can be linked by a polyethylene glycol linker..." Office Action at page 7, last paragraph. The PTO concluded that

> Agrawal *et al.* do not explicitly disclose an embodiment wherein the RNA is 21 nucleotides in length but it would be obvious to one of ordinary skill in the art to make such an oligonucleotide. One of ordinary skill in the art would recognize that producing an oligonucleotide of 21 nucleotides is a matter of design choice based on the disclosure in Agrawal *et al.* that the self-stabilized oligonucleotides can be up to 50 nucleotides in length and the target hybridizing and self-complementary regions can be of identical length and the recognition that antisense oligonucleotides are generally around 17-25 nucleotides in length.

Id.

Applicants disagree that one of ordinary skill in the art would recognize that producing a dsRNA consisting of two separate strands, where the strands are chemically linked, and where the dsRNA is 21 base pairs in length and where the dsRNA specifically inhibits the expression of said mammalian target gene, would be obvious from the disclosure of Agrawal *et al.*

Agrawal *et al.* is clearly about oligonucleotides having a hairpin structure, for the purpose of rendering the oligonucleotides resistant to degradation, and not about oligonucleotides comprising two separate and complementary RNA strands. Agrawal *et al.* states at page 5, lines 2-4, that "[t]he invention relates to novel therapeutic agents used in the antisense oligonucleotide therapeutic approach...Oligonucleotides according to the invention form stable hybrids with target sequences under physiological conditions, activate RNase H and produce only nucleosides as degradation product."

The oligonucleotides of Agrawal *et al.* require a "self-complementary" region. Self-complementary, in this context, means that two parts of the same strand form a duplex. This necessarily requires a hairpin structure, even in those embodiments where the self-complementary region is connected to the target hybridizing region by a non-nucleic acid linker. See Agrawal *et al.* at page 15, lines 1-11. Applicants claimed dsRNAs do not include a "self-complementary region," and accordingly do not include hairpin structures. Applicants' claimed dsRNAs require complementarity between two separate RNA strands. There is no "self-complementary" region included in the claimed dsRNAs.

The key to supporting any rejection under 35 U.S.C. § 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. See MPEP 2141(III) and MPEP 2143. The PTO stated that the recognition that antisense oligonucleotides are generally around 17-25 nucleotides in length would lead one of skill in the art to a dsRNA as claimed (*i.e.*, a dsRNA 21 nucleotides in length). See Office Action at page 8. Applicants disagree with this conclusion.

First, the only length restriction in Agrawal *et al.* is at page 10, lines 2-6, which states that an oligonucleotide sequence that is complementary to a nucleic acid sequence is intended to

mean an oligonucleotide sequence of from 2 to about 50 nucleotides. There is no disclosure in Agrawal *et al.* of the preferred 17-25 length range recited by the PTO, and even if there were, there is no suggestion that the particular self-stabilizing variety of oligonucleotides should have a double-stranded region of 17-25 base pairs in length.

Second, the PTO is relying on the "self-stabilizing" regions of Agrawal's *et al.* disclosure to arrive at the dsRNA structure recited in the claims. See the Office Action at page 7, which cites Agrawal *et al.* at page 15, line 26, through page 17, line 12. With respect to these self-stabilized oligonucleotides, Agrawal *et al.* states that "In a preferred embodiment, there are about 10 intramolecular base-pairs formed in the self-stabilizing oligonucleotide, with 10 base pairs being consecutive and involving the 3'-most nucleotides." Agrawal *et al.* at page 15, lines 23-26. There is nothing in Agrawal *et al.* to lead one of ordinary skill in the art to a self-stabilized oligonucleotide having 21 base pairs. Thus, even if Agrawal's *et al.* self-stabilized oligonucleotides rendered obvious a dsRNA having two separate RNA strands linked by a chemical linker (and Applicants maintain that they do not), the disclosure of Agrawal *et al.* would not lead one of skill in the art to a dsRNA 21 base pairs in length.

In KSR International Co. v. Teleflex Inc., 127 S. Ct. 1727, 1740-1741 (2007), the Supreme Court reaffirmed that the fact finder must identify and make explicit some reason that one of ordinary skill would have derived the claimed invention from elements taught in the art. This concept is consistent with Patent Office policy as set forth at MPEP 2141, which states that in view of all factual information, the Examiner must make a determination whether the claimed invention "as a whole" would have been obvious to that person at the priority date. The Examiner has not adequately explained how one of ordinary skill in the art would have arrived at the structural requirements of the claims.

The Federal Circuit in Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 83 USPQ2d 1169 (Fed. Cir. 2007), applied the current obviousness standard to the chemical arts. In Takeda the Federal Circuit held that

> [I]n order to find a prima facie case of unpatentability in such instances, a showing that the "prior art would have suggested making the specific molecular modification necessary to achieve the claimed invention" was

> also required...That test for prima facie obviousness for chemical compounds is consistent with the legal principles enunciated in KSR.

Id. at 1356.

In the present situation, there is nothing in Agrawal *et al.* that would lead one of ordinary skill in the art to a dsRNA having the claimed structural features.

In view of the foregoing, Applicants respectfully request withdrawal of the rejection of claims 16-18 under 35 U.S.C. § 103 as being obvious in view of Agrawal *et al.*

Claims 4 and 6-9 were rejected as being obvious over Crooke. As discussed above, Crooke discloses the use of modified single stranded antisense RNAs for inhibiting target gene expression. There is no teaching or suggestion in Crooke to use a double-stranded RNA to silence gene expression as required by the claims. The claims are therefore not obvious in view of Crooke, and Applicants respectfully request that the rejection of claims 4 and 6-9 under 35 U.S.C. § 103 also be withdrawn.

Applicants believe the claims are in condition for allowance, and notice to this effect is respectfully requested.

No fees are believed to be due. Any necessary charges, or any credits, should be applied to Deposit Account No. 50/2762, referencing Attorney Docket No. A2038-706120.

Respectfully submitted,

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